Risk of cardiovascular events associated with selective COX-2 inhibitors
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Authors' objectives
To analyse the randomised trials that have been performed to determine whether selective cyclooxygenase 2 (COX-2) inhibitors are associated with a protective or hazardous effect on the risk of cardiovascular events.

Searching
MEDLINE was searched from January 1998 to February 2001 for publications in the English language. The keywords used were 'COX-2', 'cyclooxygenase', 'rofecoxib' and 'celecoxib'. The same keywords were used to search the World Wide Web. The Adverse Events Reporting System (limited to the United States) was searched on October 12, 2000, for events related to rofecoxib and celecoxib. The search terms used were listed in the paper.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion. The review included published data and unpublished data submitted to the Food and Drug Administration (FDA).

Specific interventions included in the review
The authors did not state any inclusion or exclusion criteria relating to the interventions, other than the inclusion of all COX-2 inhibitors. The COX-2 inhibitors included in the review were rofecoxib (12.5 or 50 mg/day) and celecoxib (8,000 mg/day). The comparator treatments were naproxen (1,000 mg/day), ibuprofen (2,400 mg/day), nabumetone (1,000 mg/day), diclofenac (150 mg/day) and placebo. In one study, patients requiring aspirin for cardiac reasons were excluded, while in other studies, the use of aspirin was allowed.

Participants included in the review
Arthritis. No inclusion or exclusion criteria relating to the patients were given. The patients included in the review had rheumatoid arthritis or osteoarthritis. No information on the age or gender of the patients was given. Patients with cardiovascular disease were excluded in one study, while those requiring aspirin for cardiac reasons were excluded in another.

Outcomes assessed in the review
The trials had to report cardiovascular adverse events to be included in the review. The definitions of those events included in 'cardiovascular events' were not given, although the authors did list which events were considered as outcomes in each study. These included myocardial infarction (MI), unstable angina, cardiac thrombus, resuscitated cardiac arrest, sudden or unexplained death, ischaemic stroke, and transient ischaemic attacks. The main outcome assessed was all thrombotic or embolic cardiovascular events. One study presented the results separately for MI, stroke and death, but did not present the results for all cardiovascular events.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
The authors do not state that they assessed validity.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction.
The following data were presented: study name, the number of patients, treatment groups, outcomes and results. The results were reported in the included studies as the cumulative incidence, relative risks (RRs), the proportion of patients with events, and the annualised MI rate.

Methods of synthesis
How were the studies combined?
The results from the studies were not combined. The results from each study were considered separately in a narrative discussion.

How were differences between studies investigated?
Some differences between the studies were described in the text.

Results of the review
Four RCTs with a total of 18,064 patients were included. Case reports of cardiovascular events in 144 and 159 patients taking celecoxib and rofecoxib, respectively, were described.

In one large study (n=8,076), the RR of developing a cardiovascular event in patients taking rofecoxib, compared with naproxen, was 2.38 (95% confidence interval, CI: 1.39, 4.00, P<0.001). In the subgroup analysis, the RR was 4.89 (95% CI: 1.41, 16.88, P<0.01) in the ‘aspirin indicated group’ (n=321) and 1.89 (95% CI: 1.03, 3.45, P=0.04) in the ‘aspirin not indicated’ group (n=7,755). It should be noted that patients requiring aspirin for cardiac reasons were excluded from this trial. Events termed ‘serious’ by the FDA occurred in 111 rofecoxib patients and 50 naproxen patients.

In another large study (n=8,059), there was no significant difference in the rates of cardiovascular events for celecoxib compared with ibuprofen or diclofenac. The proportions of patients with events were shown graphically, stratified according to aspirin use.

Two small studies reported 3 and 9 cardiovascular events, respectively. The proportion of cardiovascular events in patients taking rofecoxib, nabumetone or placebo were 0.2, 0.4 and 0%, respectively, in one trial (n=1,042) and 1.5, 0.5 and 0.5% in the other (n=978). No statistical inference was reported regarding differences between the groups.

The authors made an indirect comparison of the annualised MI rate between the placebo arm of an existing meta-analysis of primary prevention of cardiovascular events, and the two larger trials included in this review. The rates were 0.52, 0.74 and 0.80 among patients taking placebo, rofecoxib and celecoxib, respectively. The authors point out that rheumatoid arthritis increases the risk of MI, making inter-trial comparisons difficult.

Authors’ conclusions
There was a potential increase in cardiovascular event rates for the presently available COX-2 inhibitors. Concomitant use of aspirin may not fully offset the risk of selective COX-2 inhibitors.

CRD commentary
This review addressed a clearly stated research question. The interventions and study designs included were stated, but no inclusion or exclusion criteria were specified for the participants. The definition of the outcomes included in the review was nonspecific.

The search was limited to one database (MEDLINE) and English language publications. It is therefore possible that relevant trials were missed. The search was limited to the period 1998 to 2001. The authors do not state whether COX-2 inhibitors were licensed for use in countries other than the United States during this period. The validity of the studies was not assessed. The authors do not highlight which of the studies provided better quality evidence, other than noting that two of the studies were small. The primary data reported in the review were insufficient; in particular, no information on the age and gender of the included patients was given. This may affect the interpretation of the results if the adverse effects of COX-2 inhibitors is different in different subgroups of the population.
The data in this review were not pooled. This is appropriate as the authors state that the patient groups were heterogeneous.

The authors point out that the included trials were not designed to specifically investigate cardiovascular outcomes. In the light of these comments, the conclusions of the authors are suitably conservative.

**Implications of the review for practice and research**

Practice: The authors urge caution in prescribing COX-2 inhibitors to patients at risk of cardiovascular morbidity.

Research: The authors state that definitive evidence of an increase in cardiovascular event rates will require a prospective RCT, and that it is mandatory to conduct a trial specifically assessing the cardiovascular risk and benefit of COX-2 inhibitors.

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